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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/484,964	01/18/2000	Edward T. H. Yeh	UTSH.248	1333

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EXAMINER	
BECKERLEG, ANNE M	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/484,964	Applicant(s) YEH, EDWARD T. H.
	Examiner Anne M Beckerleg	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73-75,85-92 and 94-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73-75,85-92 and 94-101* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's amendment and response received on 3/12/02 has been entered. Claims 76-84 and 93 have been canceled. Claims 73-75, 85-92, and 94-101 are pending in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in previous office actions.

Claim Rejections - 35 USC § 112

The rejection of pending claims 73-75, 86-92, and 94-101 under 35 U.S.C. 112, first paragraph, for lack of written description is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant's original claims recited a nucleic acid segment encoding a human sentrin-1 polypeptide. The claims as amended now recite a nucleic acid segment encoding a human sentrin-1 polypeptide, wherein the segment encodes at least 100 contiguous amino acids of SEQ ID NO:2, or at least 100 contiguous nucleotides of SEQ ID NO:1. It is noted that the full sequence of human sentrin-1 disclosed by the specification is 101 amino acids long.

The applicant argues that since the applicant has provided the full length sequence of human sentrin-1 polypeptide, SEQ ID NO:2, and the cDNA sequence which encodes the human sentrin-1 polypeptide, SEQ ID NO:1, the applicant has met the burden under 112 for describing the instant invention. The previous office action stated that the specification does not provide a sufficient written description for a human sentrin-1 gene or polypeptide which has a nucleotide sequence other than SEQ ID NO:1 or an amino acid sequence other than SEQ ID NO:2. Thus, the office does not dispute that the specification provides a written description of human sentrin-1 which has an amino acid sequence of SEQ ID NO:2 or a nucleotide sequence of SEQ ID NO:1. The issue in regards to written description is whether the specification has provided sufficient written description for any other amino acid or nucleic acid sequence which encodes a human sentrin-1 polypeptide. While the specification discloses several properties of the human sentrin-1 protein (SEQ ID NO:2) encoded by SEQ ID NO:1, such as the ability to bind to Fas, TNFRI, or UBC9, the specification does not provide sufficient guidance as to the nucleotide or amino acid sequences, or the physical or structural properties of any gene or protein which shares these properties. Further, the specification fails to provide guidance as to the amino acid residues which are critical to the observed biological activities of the protein corresponding to SEQ ID NO:2 such that amino acid sequences or nucleotide sequences which diverge from SEQ ID NOS: 1 or 2 and which encode a human sentrin-1 polypeptide can be determined from among the numerous possible nucleotide or amino acid sequences which encode at least 100 contiguous nucleotides or amino acids of SEQ ID NOS:1 or 2 respectively. In particular, the previous office action noted

that SEQ ID NO:1 contains over 1100 nucleotides which are apparently non-coding sequence. The specification provides no guidance as to how any 100 or 200 nucleotide portion of the noncoding sequence of SEQ ID NO:1 can encode for a human sentrin I polypeptide, or provide any description of any nucleotide sequence corresponding to the non-coding sequence of SEQ ID NO:1 which encodes a human sentrin-1 polypeptide.

In addition, the claims as amended, now read on nucleic acid segments which encode a human sentrin-1 polypeptide, wherein the segment encodes at least 100 contiguous amino acids of SEQ ID NO:2 and which is at least 85-95% identical to SEQ ID NO:2 (see claims 74-75). Since SEQ ID NO:2 consists of 101 amino acids, the claims now read on human sentrin-1 polypeptides which are substantially larger than 101 amino acids. Neither the specification nor the prior art provides any teachings or description of amino acid sequences greater than 101 amino acids which encode a human sentrin-1 polypeptide.

Despite applicant's arguments to the contrary, the issues identified above and in the previous office action are indeed relevant to the claimed invention. The invention as claimed in not limited to the full length sequence of SEQ ID NO:2 or SEQ ID NO:1. The claims as written encompass an enormous number of nucleotide sequences, while the specification only teaches a single human sentrin-1 nucleotide sequence. *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). As discussed above,

the instant specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Thus, for reasons of record, the rejection of the claims is maintained.

The rejection of claims 73-75, 85-92, and 94-101 under 35 U.S.C. 112, first paragraph, for scope of enablement is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The previous office action stated that the specification, while being enabling for a method of inhibiting Fas or TNFRI mediated apoptosis in cells in vitro comprising transfecting said cells with a nucleic acid expression construct encoding a nucleic acid comprising SEQ ID NO:1, does not reasonably provide enablement for methods of inhibiting any apoptotic pathway in cells in vitro or in vivo by administering any vector encoding any portion of the nucleic acid or amino acid sequence of SEQ ID NO:1 or SEQ ID NO:2 respectively.

The applicant argues that the in vitro results presented in the specification provide a reasonable correlation with the claimed methods and that undue experimentation is not required, citing *In re Wright* and *In re Fisher*. The applicant also argues that the office has not presented any evidence of why sentrin would not achieve inhibition of apoptosis, citing *In re Marzochhi*. 35 U.S.C. 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art. *In re Fisher*,

166 USPQ 18, 24 (CCPA 1970). Contrary to applicant's arguments, the previous office action analyzed the specification in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement for the instant methods. It is also noted that case law including the Marzocchi decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see *In re Marzocchi* 169 USPQ 367, and *Ex parte Sudilovsky* 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). Ultimately, case law states that ".. the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

The specific issues discussed in the previous office action are reiterated for applicant's convenience. The specification does not provide an enabling disclosure for inhibiting any apoptotic pathway in any cell in vitro or in vivo using any portion of a human sentrin-1 polypeptide or the full length human sentrin-1 nucleic acid or polypeptide. The art at the time of filing teaches that several different apoptotic pathways exist in the cell which can be triggered by substantially different stimuli (Lavin et al., and Lieberthal et al). The specification teaches that

while human sentrin-1 can bind to the death domains of Fas and TNFRI, it does not bind to CD40 or FADD/MORT1 (specification, page 53, lines 25-29). While the specification does provide additional working examples which disclose the ability of sentrin-1 to bind to various other proteins, such as UBC9, ranGAP1 or PML, it does not provide any evidence that this binding results in the inhibition of apoptosis in a cell. The specification suggests that sentrin interacts with these protein in a process similar to ubiquitination. Neither the specification nor the art at the time of filing teaches that the process of protein ubiquitination results in the inhibition of apoptosis. At the time of filing, it was well known that protein ubiquitination usually results in protein degradation. Thus, in view of the numerous different apoptotic pathways, applicant's demonstration that sentrin-1 does not bind to FADD/MORT1 or CD40, the lack of correlation between the binding of sentrin to UBC9 , ranGAP1 or PML and any effect on apoptosis, and the breadth of the claims, it would have required undue experimentation to practice the scope of the instant invention as claimed and the skilled artisan would not have predicted success in inhibiting any apoptotic pathway in a cell by providing the cell with a nucleic acid encoding human sentrin.

The specification does not provide an enabling disclosure for the inhibition of Fas or TNFRI induced apoptosis in any cell in vitro or in vivo using any portion of a human sentrin-1 nucleic acid or polypeptide. The specification, as discussed above, provides evidence that the full length human sentrin -1 nucleic acid sequence encodes a polypeptide which when expressed in a murine or human cell is capable of inhibiting to a greater or lesser degree Fas or TNFRI mediated apoptosis. The specification, while disclosing that portions of the nucleic acid sequence of a

human sentrin or specifically of SEQ ID NO:1 can be used to inhibit apoptosis, does not provide sufficient guidance as to which portions, of the numerous possible nucleic acid sequences which may comprise 50 or more contiguous nucleotides of SEQ ID NO:1 or which may encode 20 or more contiguous amino acids of SEQ ID NO:2, retain the apoptosis inhibiting activity of the full length human sentrin -1 polypeptide, SEQ ID NO:2, encoded by SEQ ID NO:1. In regards to the nucleic acid sequence in SEQ ID NO:1, it is noted that first 90 and the last 1065 nucleotides of SEQ ID NO:1 do not apparently encode for any polypeptide. If any open reading frame exists in the first 90 nucleotides or the last 1065 nucleotides, the specification neither discloses the corresponding encoded amino acids or provide any guidance as to the nature or activity of any hypothetically encoded polypeptide. The specification further does not provide any guidance that the non-coding nucleotides of SEQ ID NO:1 have any anti-apoptotic activity. As the specification teaches that the anti-apoptotic activity of the human sentrin 1 polypeptide comprising the amino acid sequence of SEQ ID NO:2 is the result of protein:protein interactions, the skilled artisan would have considered it highly unpredictable whether any 50 or 100 or 200 contiguous nucleotides from the non-coding portion of SEQ ID NO:1 would have any effect on apoptosis in a cell. In addition, the specification, while suggesting that a nucleic sequence encoding any 20 up to 100 contiguous amino acids of SEQ ID NO:2 can be used to inhibit apoptosis according to the instant methods, Figure 1A demonstrates that only the full length sentrin corresponding to the entire 101 amino acids of SEQ ID NO:2 can bind to the Fas death domain. The 1-70AA sentrin fragment and the 1-23AA sentrin fragment failed to exhibit Fas binding (specification, Figure 1A).

The specification does not provide any specific guidance as to the amino acid sequence of any 20 or 30 or 40 or 50 amino acid portion of SEQ ID NO:2 which retains Fas or TNFRI binding and which is further capable of inhibiting apoptosis in a transfected cell expressing said portion. The results of Figure 1A indicate that amino acid residues 71-101 of SEQ ID NO:2 are clearly required for Fas binding. In the absence of specific guidance from the specification and in view of the results depicted in Figure 1, it is unclear which residues are essential for Fas or TNFRI binding and apoptosis inhibition and thus, the skilled artisan would not be able to predict whether any portion of the amino acid sequence of SEQ ID NO:2 would be capable of retaining the apoptosis inhibiting activity of the full length human sentrin-1 protein. Further, as discussed in the previous paragraph, while the specification provides data concerning the binding of sentrin-1 to various proteins other than Fas or TNFRI and provides some analysis of sentrin domains required for binding to UBC9 , ranGAP1 or PML, the specification has not related the "sentrinization" of these proteins with any effect on apoptosis. Thus, in view of the failure of the 1-70AA and 1-23AA portions of sentrin-1 to bind to Fas, the lack of guidance concerning specific portions of the sentrin polypeptide which retain Fas and/or TNFRI binding and anti-apoptotic activity, the lack of correlation between applicant's binding studies of sentrin to UBC9 , ranGAP1 or PML and any effects on apoptosis or sentrin binding to Fas or TNFRI, and the breadth of the claims, the skilled artisan not have been able to predict without undue experimentation whether any portion of SEQ ID NO:1 or a nucleic acid sequence encoding any portion of SEQ ID NO:2 would be capable of inhibiting Fas or TNFRI mediated apoptosis.

The specification also does not provide an enabling disclosure for inhibiting apoptosis in vivo by directly administering any vector encoding human sentrin-1. The specification discloses that a pharmaceutical composition comprising a nucleic acid encoding sentrin-1 can be administered to a mammal in order to inhibit apoptosis. The specification does not disclose any disease or condition associated with apoptosis. Further, the specification fails to provide any guidance concerning the characteristics of cells to be targeted for apoptosis inhibition, the level of sentrin expression from any vector in such a target cell which correlates with apoptosis inhibition, the routes and dosages of administration of any vector encoding sentrin to a mammal such that the target cells or organs are transfected, or the level and duration of apoptosis inhibition within a target cell population which correlates with any effect on any symptom of an apoptosis related disease or condition. At the time of filing, in vivo gene therapy utilizing the direct administration of recombinant nucleic acids, whether in the form of retroviruses, adenoviruses, or adeno-associated viruses, was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, ".. difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states in a report to the NIH that, "

.. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 1, paragraph 3, and page 8, paragraph 2). Among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are anti-viral immune responses, and the identity of the promoter used to drive gene expression. Thus, the art at the time of filing clearly establishes that the expectation for achieving a desired therapeutic effect in vivo by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

In regards to applicant's arguments regarding clinical trials and in particular clinical trials with adenoviral vectors, it is noted that the applicant's claims are not limited to adenoviral vectors, and that the initiation of phase I clinical trials does not indicate that the skilled artisan either at the time of filing or at present regarded gene therapy as either predictable or routine. Verma et al., Marshall et al, and Orkin et al., all cited in the previous office action and discussed above, summarize the state of the art of gene therapy at the time of filing as highly unpredictable. Therefore, in view of the art recognized high level of unpredictability in treating disease using recombinant vectors at the time of filing, the lack of guidance provided by the specification for the parameters affecting vector delivery and gene expression in vivo, the lack of correlation between

applicant's in vitro working examples and the therapeutic inhibition of apoptosis in a mammal, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Deborah Reynolds, can be reached at (703) 305-4051. General inquiries

should be directed to the group receptionist whose phone number is (703) 308-0196. The technology center fax number is (703) 308-4242, the examiner's direct fax number is (703) 746-7024.

Dr. A.M.S. Beckerleg

A.M.S. BECKERLEG
PATENT EXAMINER